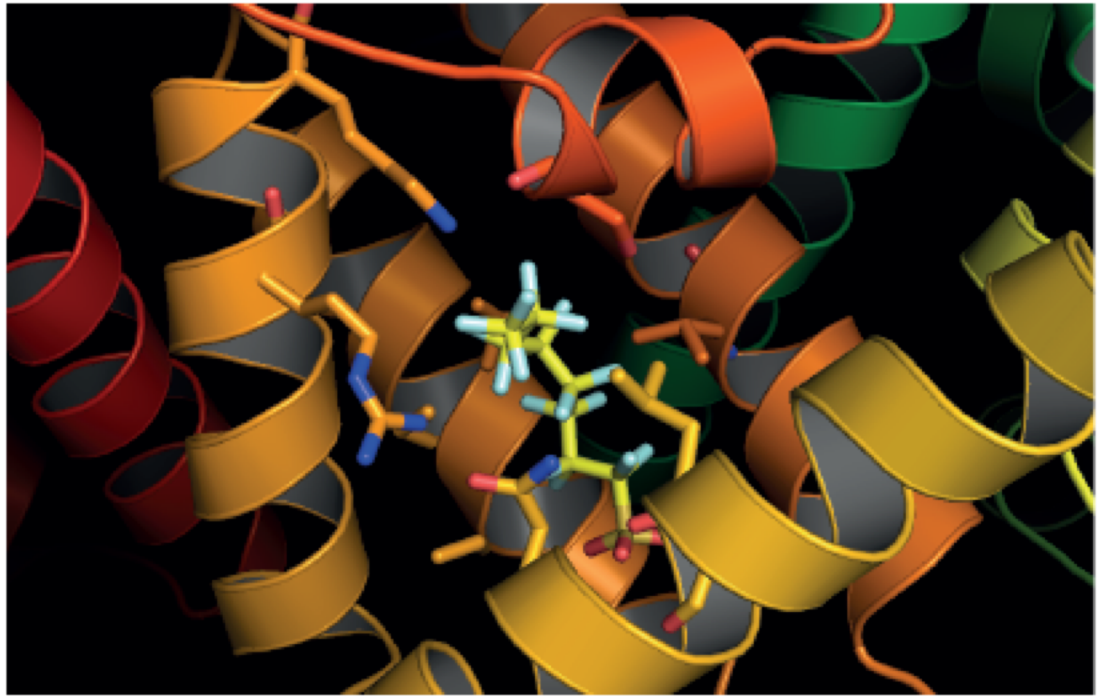
Using Molecular and Cellular Insight for Integrative Modeling of Whole-Organism Fate



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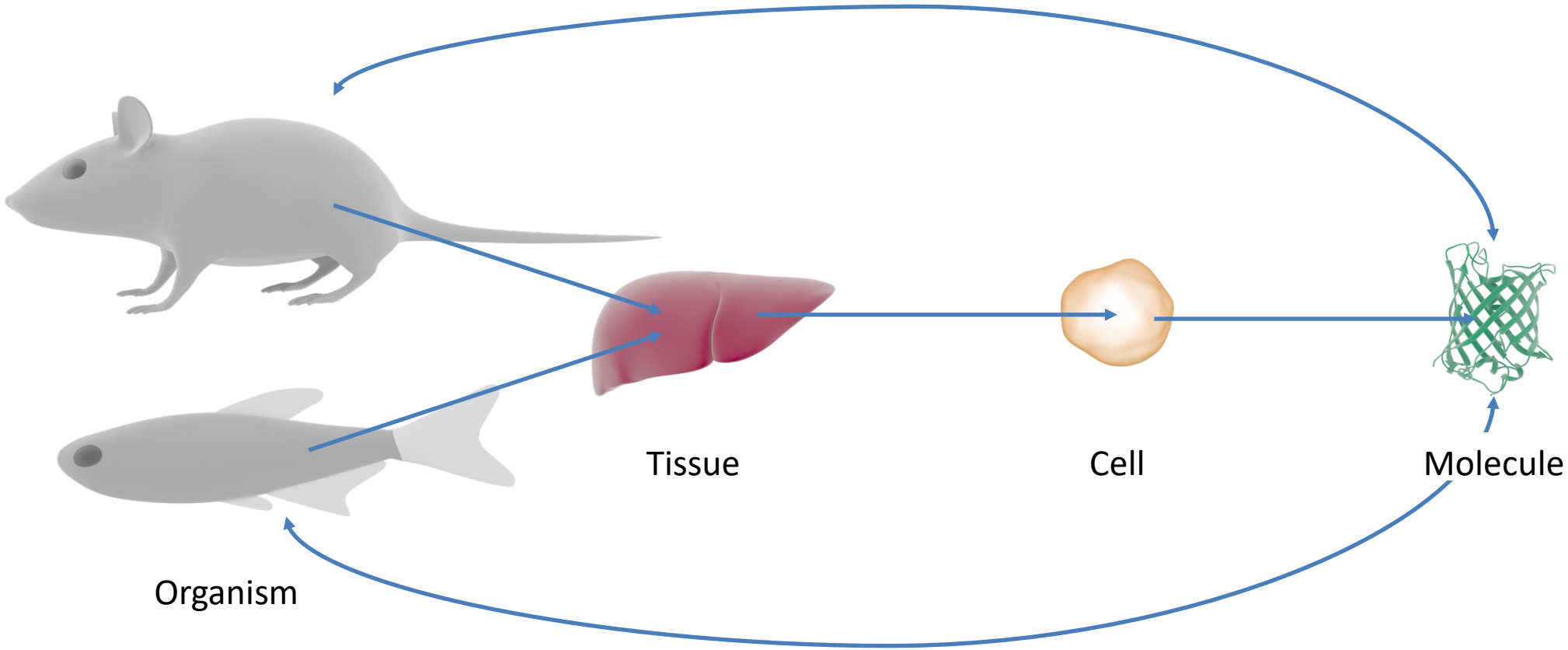
UCB SRP PFAS Workshop, 12/13/19

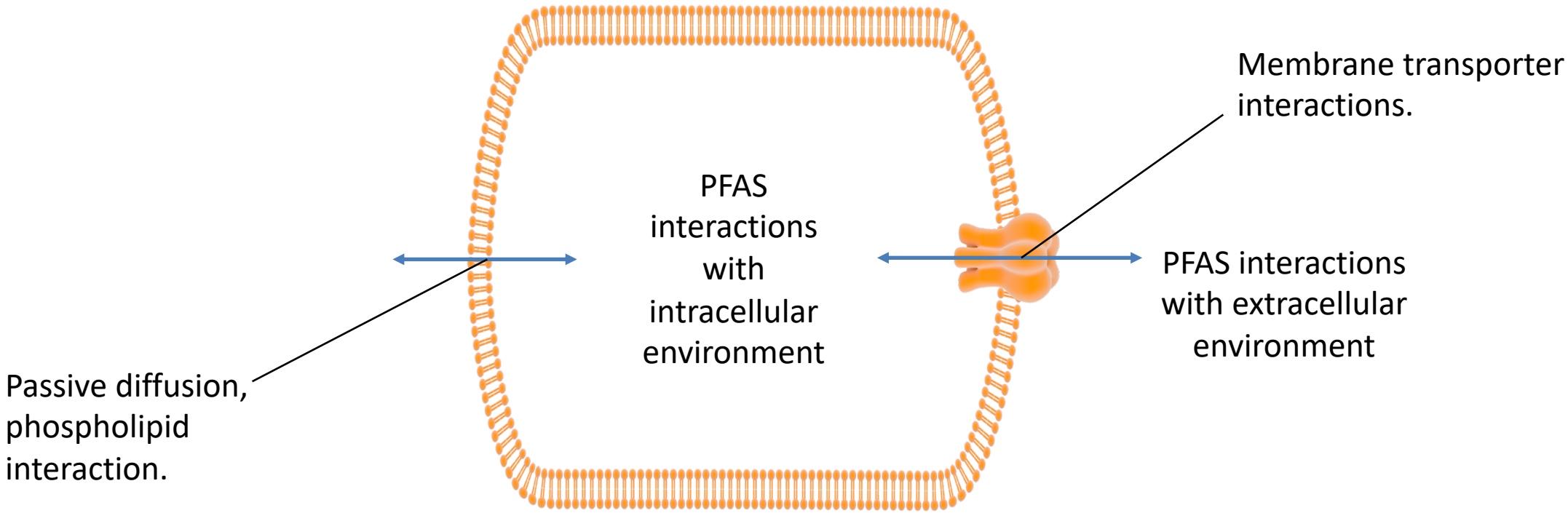
A Multi-Scale Approach



My group's approach is focused around PFAS interactions with proteins, membrane transporters and other key biomolecules.

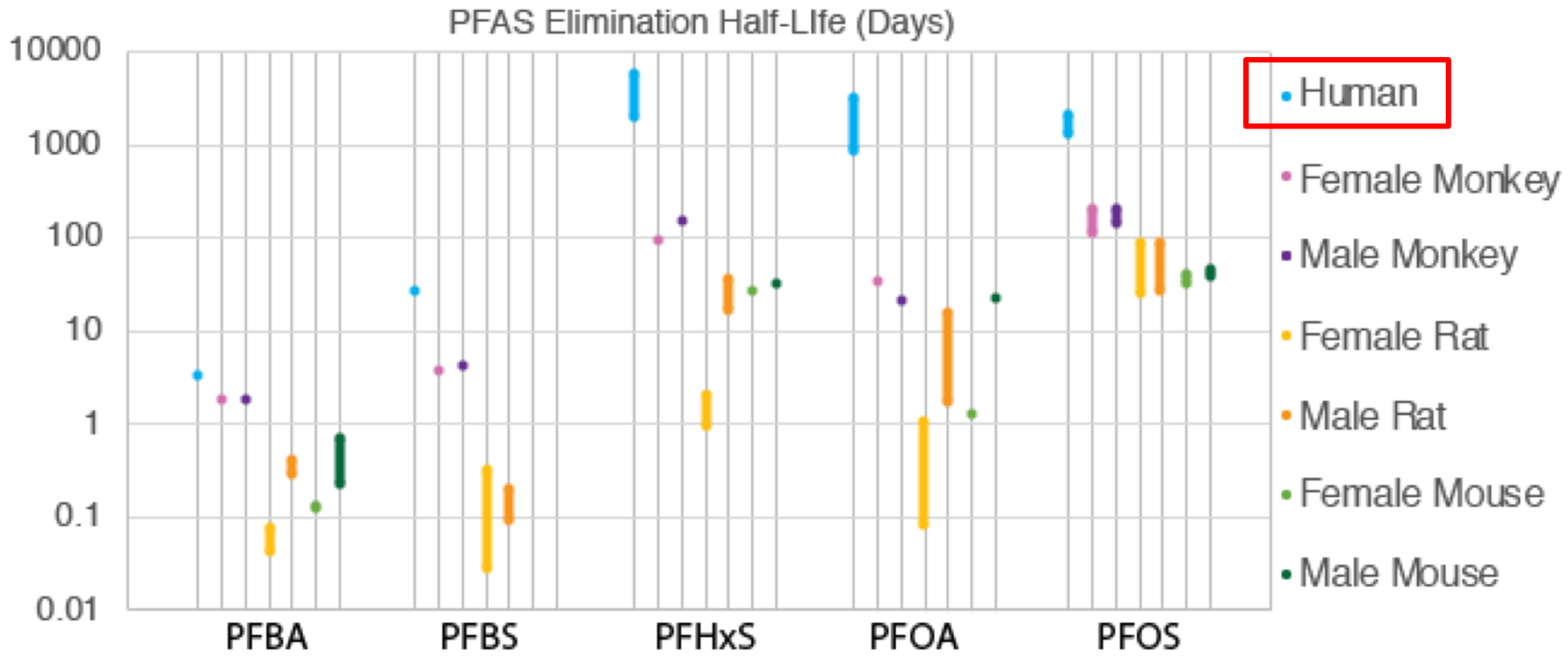
Tissue distribution: the Ins and Outs of Cells

What do we need to know?



Toxicokinetics: What's So Special About PFAS?

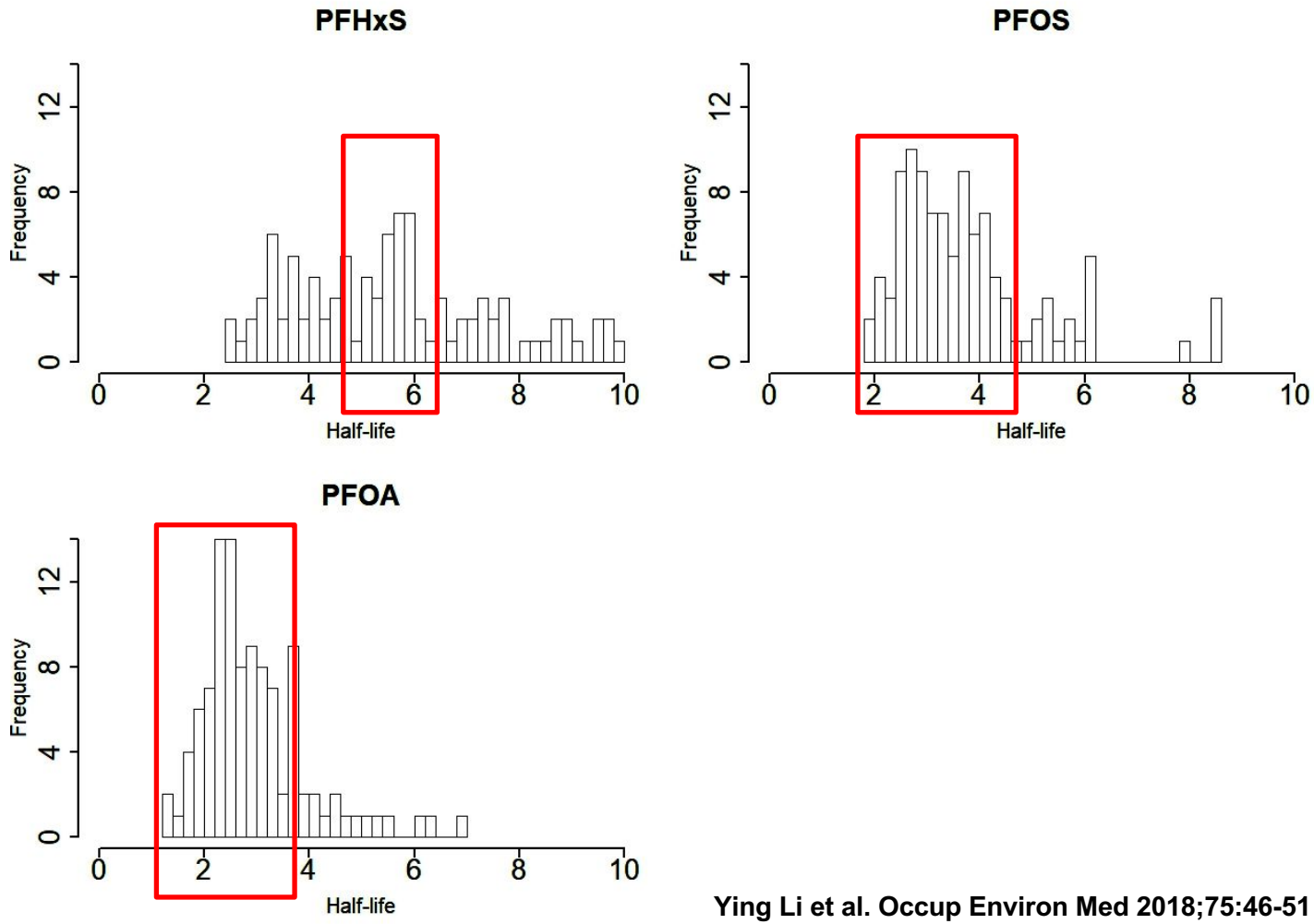
- PFAS – protein interactions affect their internal distribution (tissues where they accumulate)
- They also lead to unique and variable elimination kinetics.



Data extracted from Pizzuro et al. 2019 Reg. Toxicol. Pharmacol.

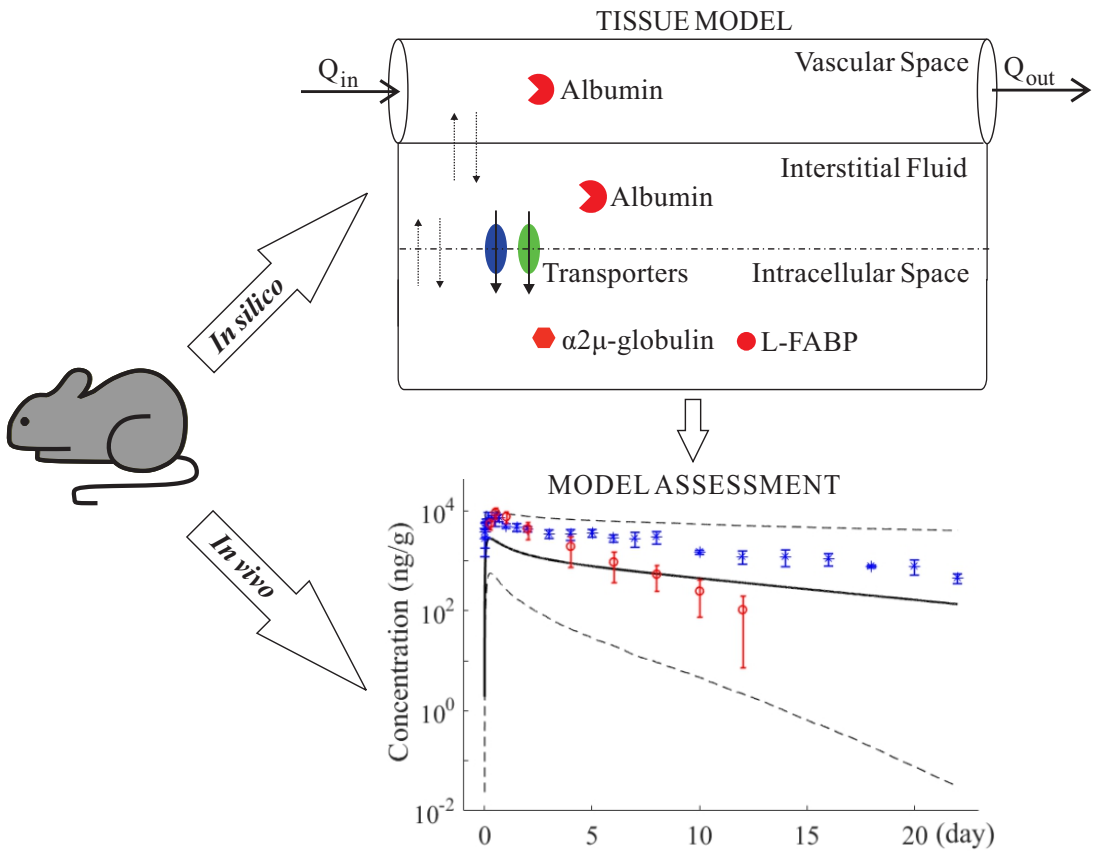
Toxicokinetics: What's So Special About PFAS?

Some PFAS have very long and highly variable lifetimes in humans.



Ying Li et al. Occup Environ Med 2018;75:46-51

Toxicokinetics: Whole-Organism Parameterization



For a relatively well-characterized PFAS (PFOA) can a PBTK model help us gain insight into key interactions and key tissues?

Weixiao Cheng

Our Approach: "Bottom-up PBTK"

<u>Components:</u>

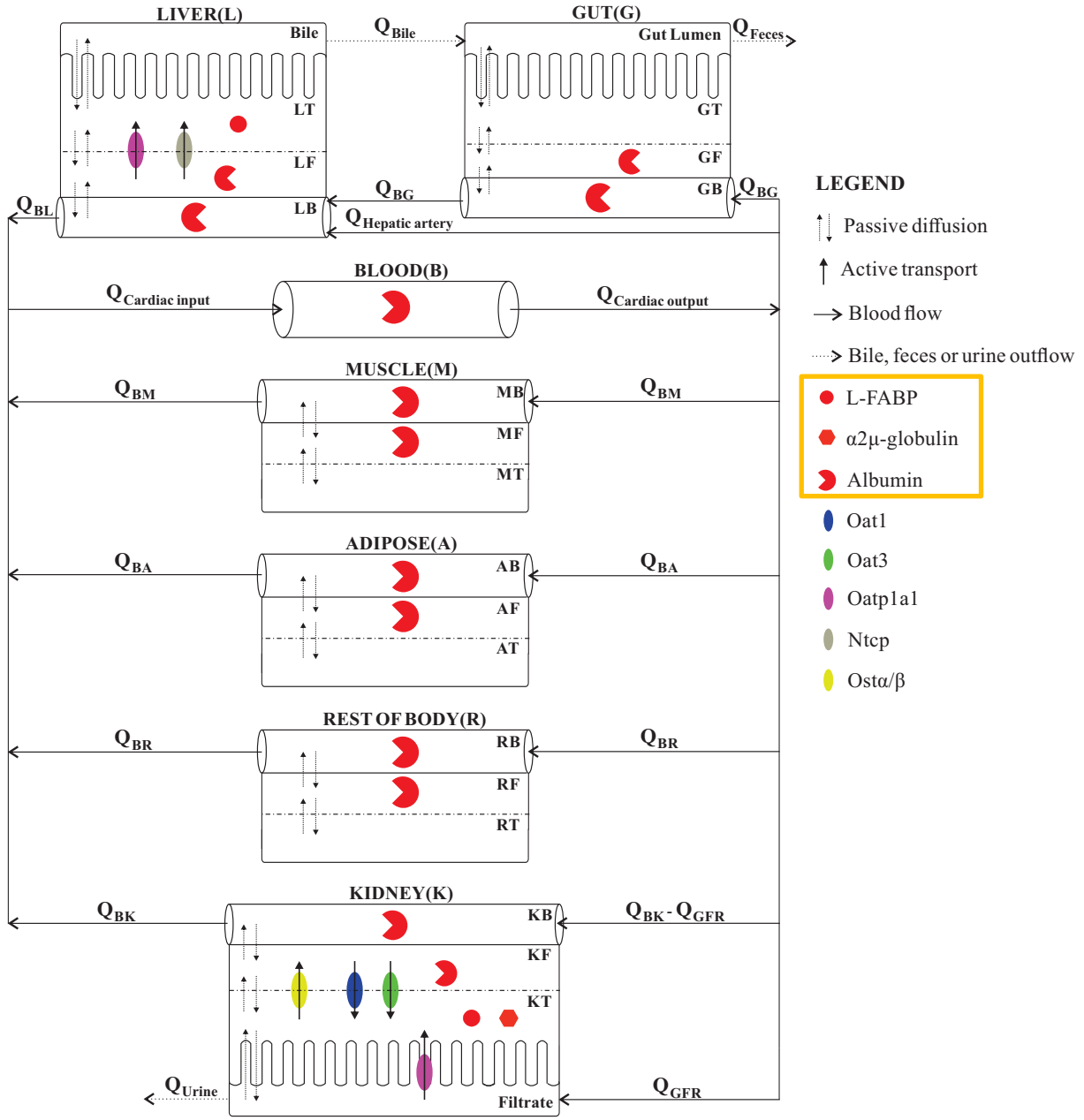
Physiology

In vitro data

<u>Goal:</u>

No parameters fit to *in vivo* data.

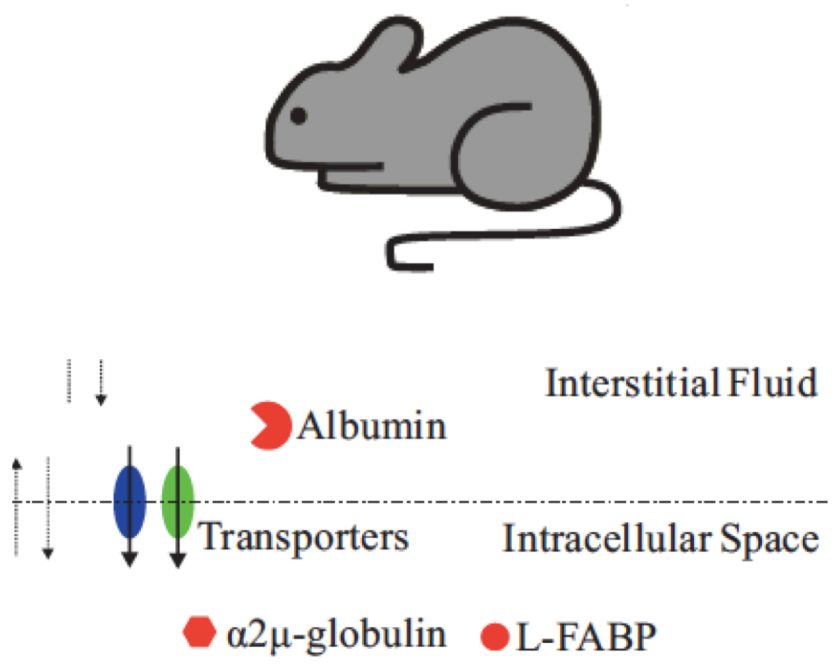
(Test of IVIVE)



Our Approach: "Bottom-up PBTK"

72 Independent Parameters

Physiology, Binding, Transport



Evaluation Data

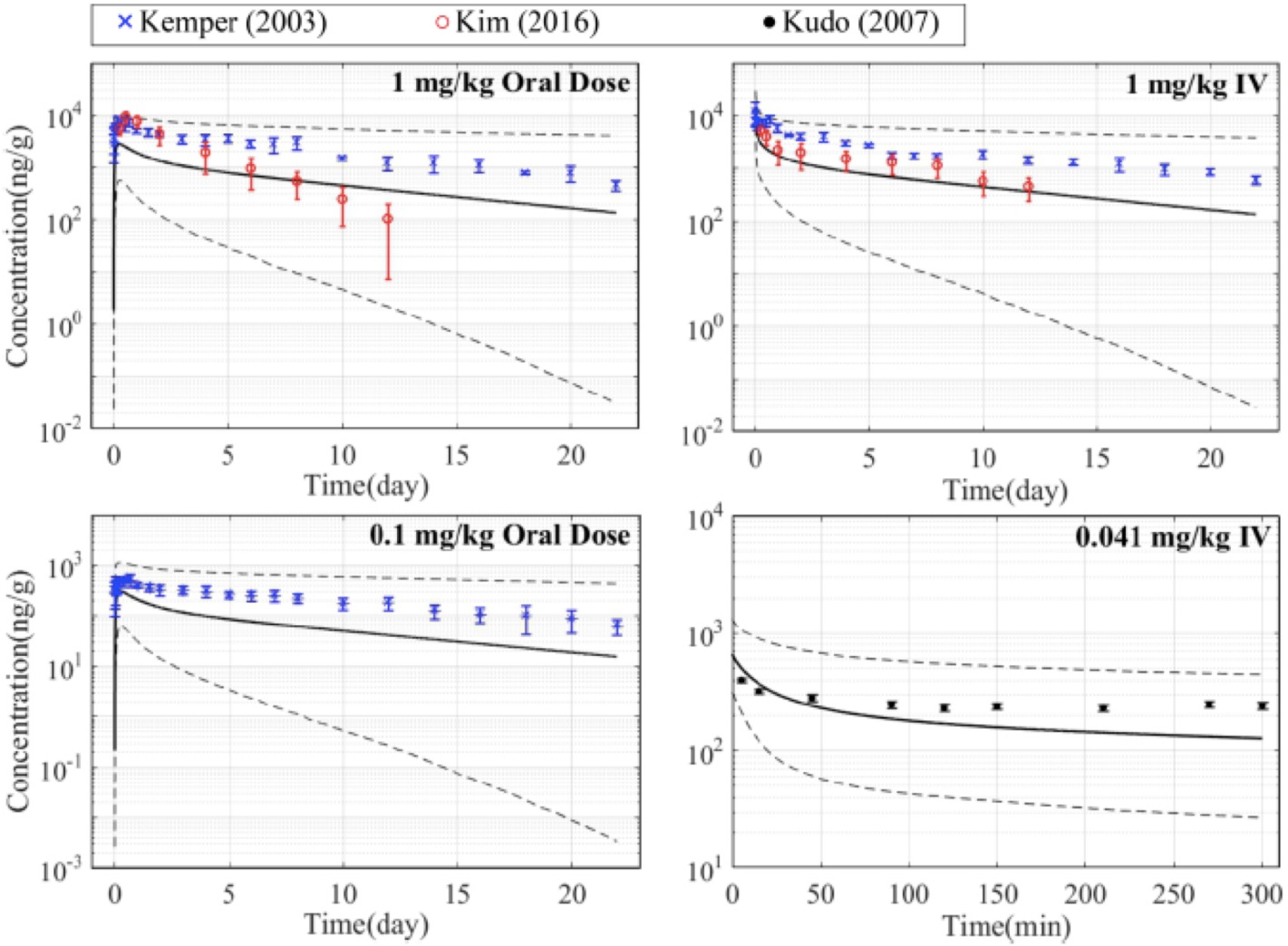
7 data sets from 3 studies:

- Kemper 2003
- Kudo et al. 2007
- Kim et al. 2016

High and low doses:
1 mg/kg, 0.1 mg/kg, 0.041 mg/kg

Oral and IV dose
Plasma time course
Tissue distribution

Serum Clearance by Dose and Exposure Route

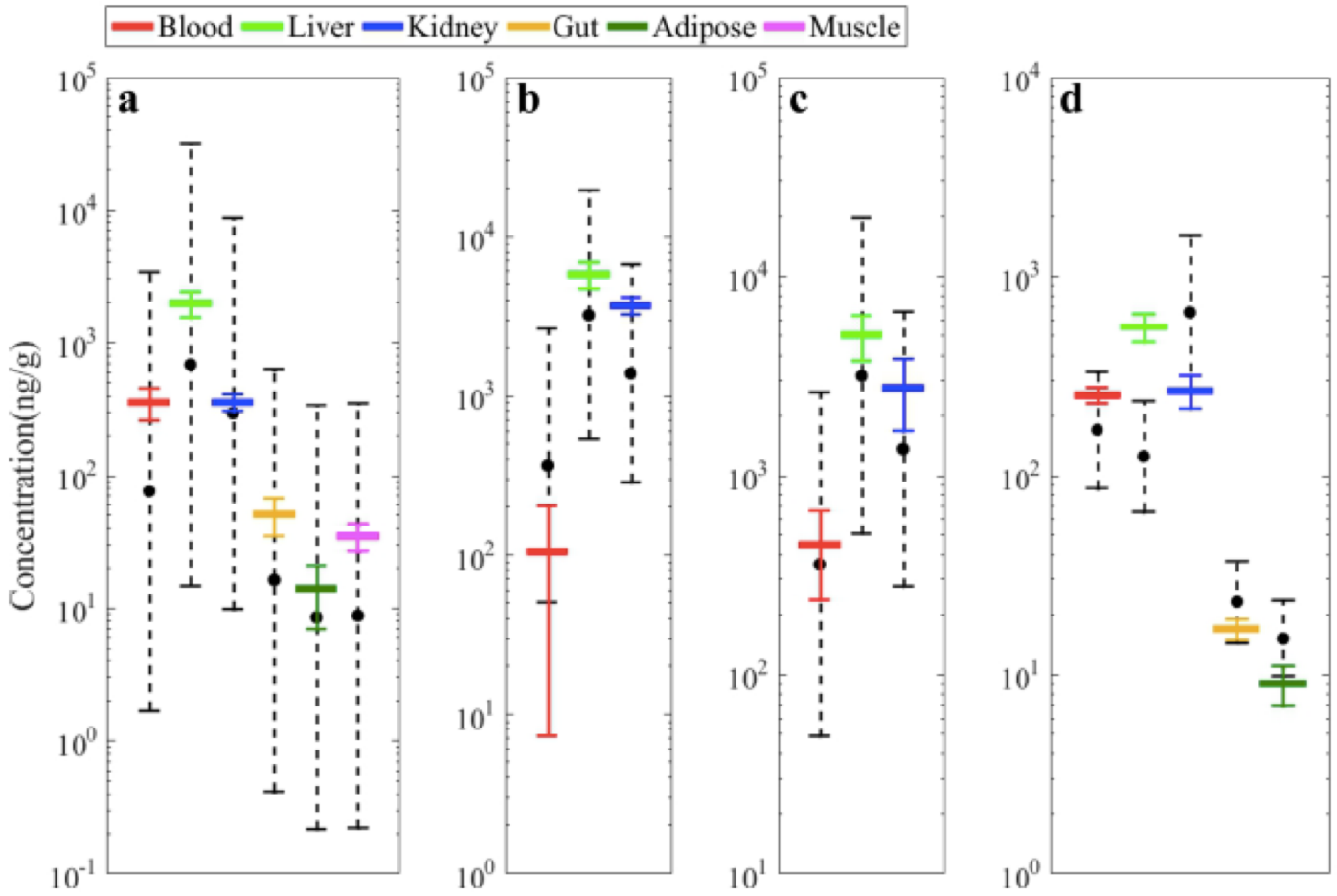


A well-parameterized model can reproduce in vivo behavior for different doses and exposure routes.

None of the model's 72 parameters were fit to time-course data. However, some are *semi-empirical*.

Cheng & Ng 2017 ES&T

Tissue distribution by dose and exposure



(a) 28d after 1mg/kg oral dose (Kemper 2003)

(b,c) 12d after 1mg/kg oral, IV dose (Kim 2016)

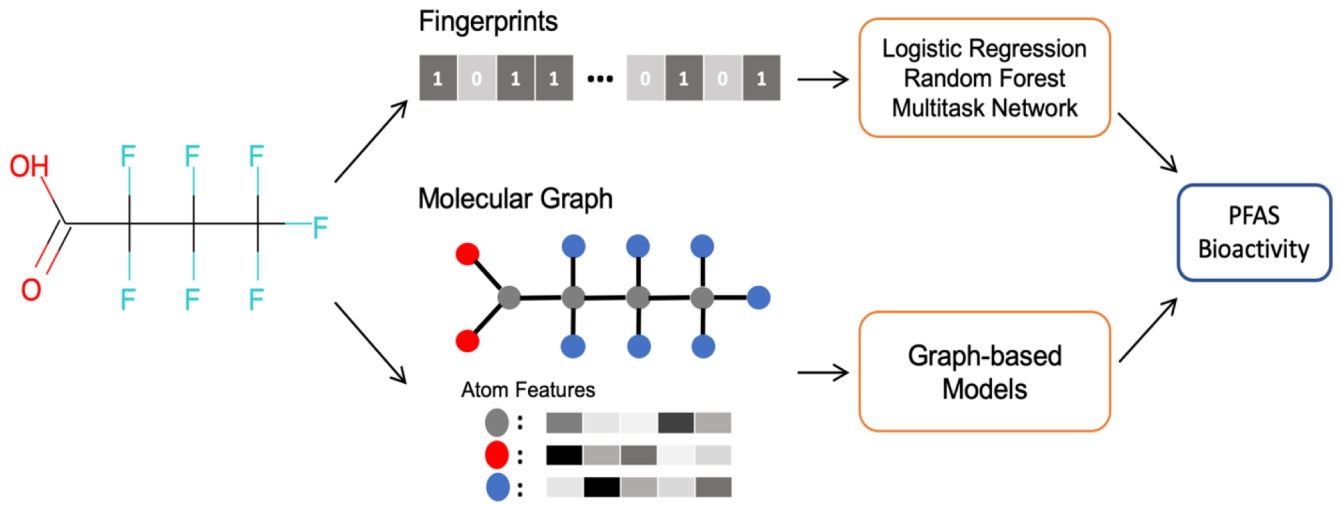
(d) **2hr** after 0.041mg/kg IV dose (Kudo 2007)

Achieving this level of model-data agreement requires knowledge of how PFOA enters cells and what mechanisms influence the length of their stay.

This knowledge is unavailable for the majority of PFAS and organisms– this is where molecular dynamics and in vitro assays can provide critical insight.

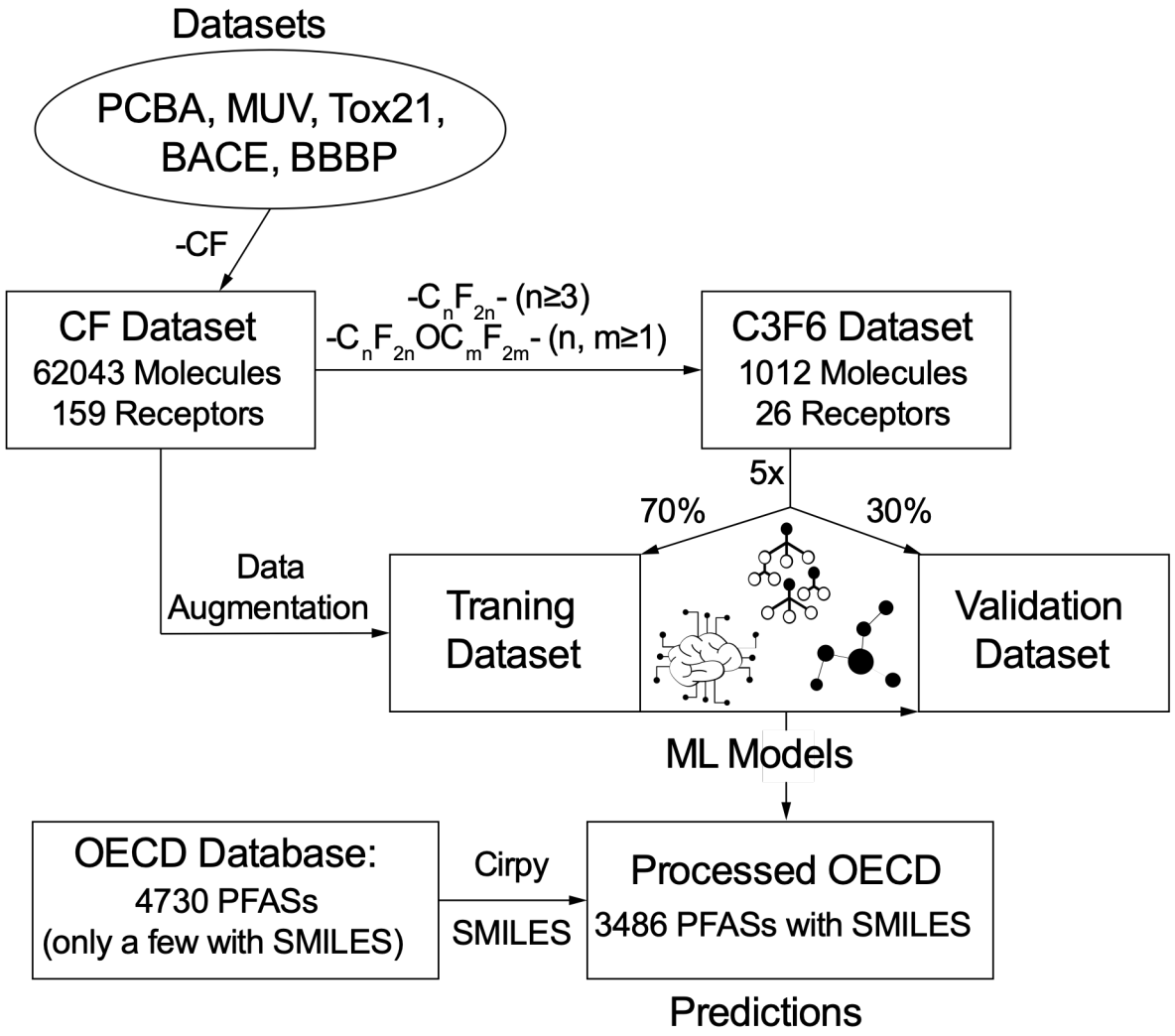
Cheng & Ng 2017 ES&T

Mapping the Iceberg: Can Big Data Approaches Help?

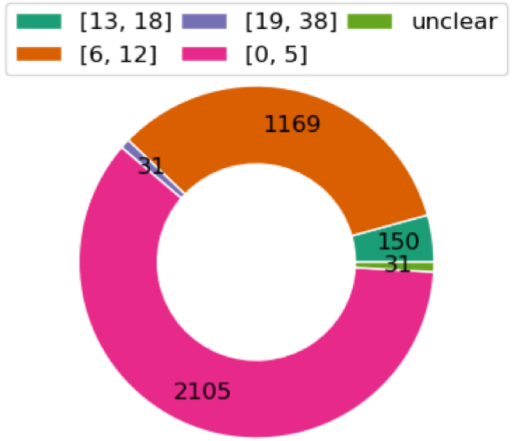


Datasets	# Molecules	# Bioassays	# Bioactivities	Active rate (%)
PCBA	60559	128	4465740	1.237 (0.002 - 51.415)
Tox21	524	12	4759	9.666 (3.363 - 23.438)
MUV	7756	17	16594	0.211 (0.077 - 0.463)
BACE	761	1	761	56.636
BBBP	285	1	285	91.228
CF	62043	159	4488139	1.257 (0.002 - 91.228)
C3F6	1012	26	14335	7.276 (2.038 - 43.000)

Mapping the Iceberg: Can Big Data Approaches Help?

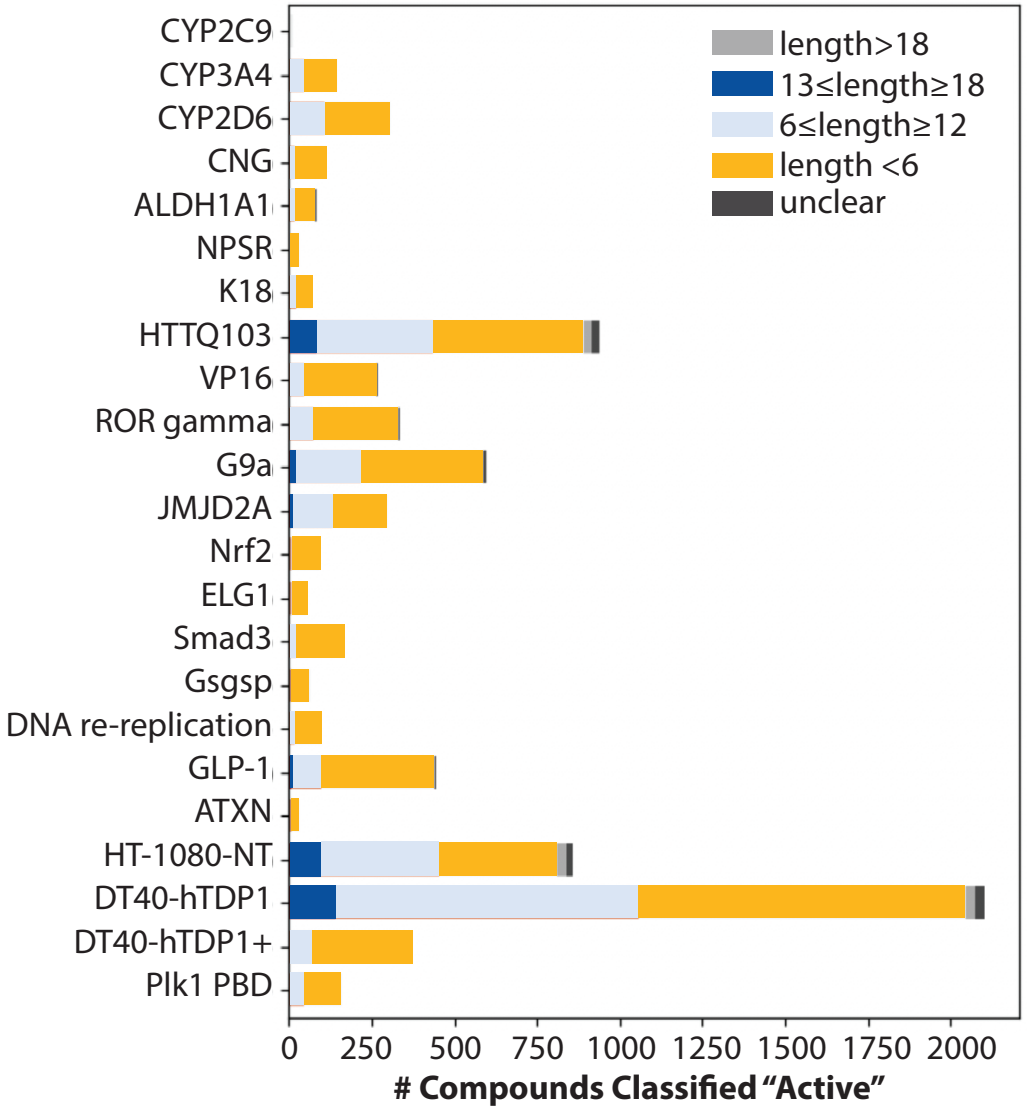


Characteristics of the OECD PFAS List

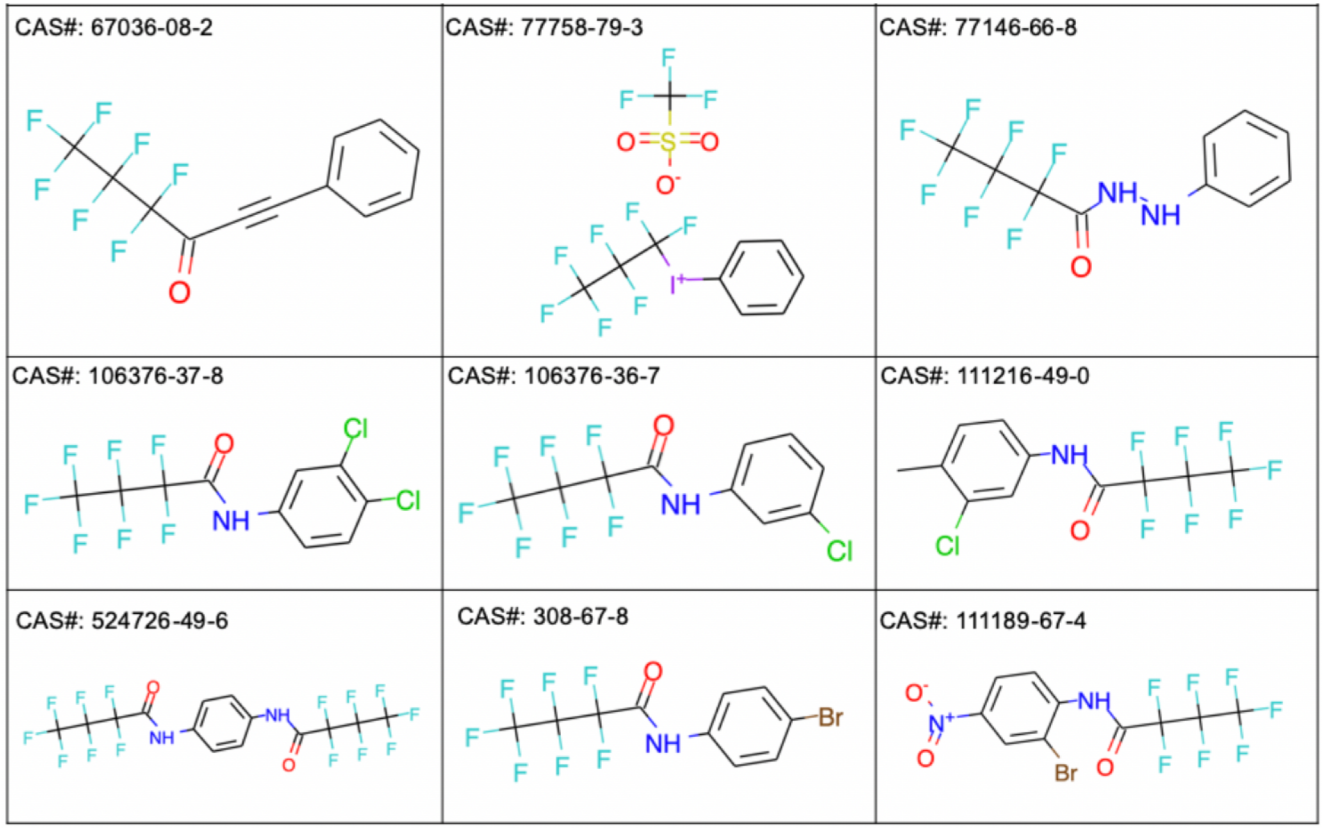


	Linear Isomer	Non-linear Isomer
Count	2688	798
	Polymer	Non-polymer
Count	4	3482
	Precursor	Non-precursor
Count	3119	367

Mapping the Iceberg: Can Big Data Approaches Help?



Cheng & Ng, *2019 ES&T*



Active rates give clues for further in silico, in vitro, in vivo studies for chemicals and their potential toxic pathways.

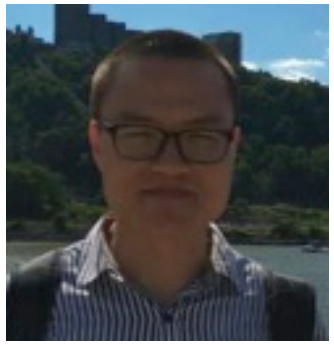
Congruence between these results and the MD results suggest opportunities for "weight of evidence."

Caveat: constrained by the definition of PFAS within the OECD set.

The Promise of Models, the Persistence Of Data Gaps

- With multiscale approaches, we can:
  - Incorporate in vitro and in silico data to predict in vivo toxicokinetics.
  - Integrate across data sources to predict toxicodynamics
  - Screen multiple PFAS to evaluate differences between “emerging” and “legacy” substances.
  - Provide insight into sex, species, and population differences in PFAS fate and effects to:
    - Identify vulnerable populations (based upon health status and/or geography)
    - Evaluate whether species are suitable “model organisms”

- But important data gaps persist:
  - Models need validation – more in vitro, in vivo (?), and biomonitoring data.
  - Processes need refinement (e.g. integrate phospholipid and protein influences).
  - From interaction to effect: toxicological piece is ongoing and important.



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SERDP

DOD ▪ EPA ▪ DOE

Grant ER18-1417

THANK YOU

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